

REMARKS

Claims 1-31 are pending. Claims 28-31 are withdrawn from consideration without prejudice. Claims 1-27 remain in the application. Applicants expressly reserve the right to pursue the withdrawn claims in a divisional application. Claim 1 is currently amended to correct a claim informality and does not in any way narrow the claim scope. No new matter is introduced.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 1-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ott *et al.* (GB 2,114,978) taken with Tomita *et al.* and Venek *et al.*

The mere fact that references can be combined does not render the resultant combination obvious. Obviousness by prior art combination "requires determination of whether there was something in the prior art as a whole suggest the desirability, and thus the obviousness, of making the combination, in a way that would produce the [claimed] structure." Continental Can Company USA, Inc. v. Monsanto Co., 948, F.2d 1264 (Fed.Cir. 1991). Because there is no motivation to combine the references and because the differences between the claimed invention and the prior art are such that the invention, as a whole, would not have been obvious to the skilled artisan at the time the invention was made, Applicants respectfully traverse.

Ott *et al.* discloses, using a fed batch technology, the preparation of a fermentation broth that contains either almost all nebramycin-5' or a mixture of nebramycin-2 and nebramycin-5' at a desired preset ratio and nebramycin-4 (Ott *et al.*, page 2, lines 27-38). Tomita *et al.* discloses, using a submerged culture, the preparing of a fermentation broth that contains apramycin and nebramycin factor V' by cultivating a strain of *Streptoalloteichus hindustanus* under submerged aerobic conditions in an aqueous medium containing assimilable sources of carbon and nitrogen (Tomita *et al.*, col. 2, lines 12-24). Neither Ott *et al.* nor Tomita *et al.*, each taken alone or in combination with each other,

discloses steps of regulating a constant level of assimilable carbon and assimilable nitrogen and recovering 6'-O-carbamoyl tobramycin. These two references are completely silent concerning a metabolic controlled feeding, let alone continuously regulating a constant level of assimilable carbon source and assimilable nitrogen source. This has been acknowledged by the Examiner when she stated "[t]he reference[s] appear to differ from the claimed invention in that the assimilable carbon and nitrogen source is not maintained constant" (Office Action, page 3, lines 7-9). There is simply no suggestion or teaching regarding a step of regulating constant levels of assimilable carbon source and assimilable nitrogen source for producing 6'-O-carbamoyl tobramycin.

In this Office Action, the Examiner alleges that:

"it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of Ott *et al.* and/or Tomita *et al.* by performing the fermentation for the production of 6'-O-carbamoyl tobramycin in a chemostat as suggested by the teachings of Vanek *et al.* to maintain constant the levels of assimilable carbon and nitrogen sources for the expected benefit of selecting strains of microorganisms or specifically of *S. tenebrarius* suitable for a process that maximizes the yield of the useful antimicrobial agent 6'-O-carbamoyl tobramycin."
(Office Action, page 3, lines 14-20)

Applicants respectfully submit that Vanek *et al.* fails to disclose a metabolic controlled fermentation **for producing 6'-O-carbamoyl tobramycin**. Instead, Vanek *et al.* only teaches using a **chemostat device to achieve selection and enrichment of active strains of microorganisms**. Use of a chemostat device permits the selection of a mutant strain having a higher specific growth rate. The periodic selection is achieved by regulating a limiting substrate so as to maintain a "continuously growing culture" for a mutant strain. Vanek *et al.* exemplifies the selection of a *E.coli* B hyper-B-D-galactosidase producing strain during limitation of the specific growth rate by lactose. According to Vanek *et al.*, the selection of a new mutant is attributed to a lower Ks and the industrial application of a chemostat is far from practical.

"A characteristic feature in the selection and accumulation in steady-state cultures in a chemostat is a **continuous and or**

periodic gradation of mutants as indicated by the terms continuous and periodic selection... **Gradual spontaneous mutations give rise to selection of new mutants with a lower K_s constant** (a parameter corresponding to the substrate concentration at which the growth rate is half maximal). This leads to the creation of their periodic selective advantage and an ensuing periodic accumulation..." (page 192, lines 17-26) (emphasis added)

"Selection and accumulation of regulation **mutants and hyperproducing mutants** synthesizing large amounts of enzymes in a chemostat is thus principally feasible. In some cases, periodic selection in a chemostat can yield qualitatively different **"genetically derived" enzymes** with favorable properties. However, this method is **far from universal and can fail, or yield unreproducible results**, especially with eukaryotic microorganisms. Among this shortcomings are **aggregation with cells** during a prolonged limited growth, followed usually by growth of cells in clusters on the walls of the cultivation vessel (Larson and Dimmick, 1964), and a **genetic instability and segregation of diploid hyperproducing strains**. These strains, synthesizing during a limited growth in a chemostat a single enzyme in an amount corresponding to 20-40% of the total amount of cell proteins, actually represent **polyploid genetic chimeras**. **This present difficulties in strain maintenance, storage, transfers, and preservation**. All these aspects **restrict** the industrial application of scale-up, in attempts at industrial-scale preparation of enzyme-active biomass by subbmerged-batch or fed-batch cultivations, as well as in a wider use of these strains as starting materials for immobilization or sources for enzyme isolation or subsequent immobilization." (page 195, lines 15-33) (emphasis added)

While Ott *et al.* and Tomita *et al.* are directed to fermentation processes for preparing nebramycin, Vanek *et al.* specifically discloses the selection of a mutant strain using a chemostat device. A skilled artisan, after reading Vanek *et al.*, would not even be invited to experiment with Ott *et al.* or Tomita *et al.* Absent some teaching or suggestion, explicitly or implicitly, found in the cited references that would motivate one of skilled in the art to regulate a constant level of assimilable carbon source and nitrogen source in a fermentation process to recover 6'-O-carbamoyl tobramycin, the *prima facie* obviousness rejection must fail.

Vanek *et al.* teaches a process of selecting a mutant strain using a chemostat device, which is entirely different from those teachings of Ott *et al.* or Tomita *et al.* Assuming *arguendo*, Vanek *et al.* were to combined with Ott *et al.* and/or Tomita *et al.*, it would at best result in selecting a hyper-strain derived from *Streptomyces tenebrarius* or *Streptoalloteichus hindustanus*.

Applicants further submit that the present invention, as a whole, is directed to a fermentation process using a metabolic controlled approach (i.e., regulating a constant level of assimilable carbon source and nitrogen source). Because the prior art of record did not recognize that a controlled metabolic regulation effective in production of 6'-O-carbamoyl tobramycin, Applicants submit that they do not render Applicants' invention as a whole obvious.

The cases of In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988), and In re Jones, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992), also make plain that the Office Action's assertions that it would have been obvious to modify the reference relied upon does not properly support a § 103 rejection. It is respectfully suggested that those cases make plain that the Office Action reflects a subjective "obvious to try" standard, and therefore does not reflect the proper evidence to support an obviousness rejection based on the references relied upon. In particular, the Court in the case of In re Fine stated that:

Instead, the Examiner relies on hindsight in reaching his obviousness determination. . . . **One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.**

In re Fine, 5 U.S.P.Q.2d at 1600 (citations omitted; emphasis added). Likewise, the Court in the case of In re Jones stated that:

Before the PTO may combine the disclosures of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the

Appl. No. 10/047,693
Amdt. Dated May 13, 2004
Reply to Office Action of November 13, 2003

knowledge generally available to one of ordinary skill in the art. . . .

Conspicuously missing from this record is any evidence, other than the PTO's speculation (if it be called evidence) that one of ordinary skill . . . would have been motivated to make the modifications . . . necessary to arrive at the claimed [invention].

In re Jones, 21 U.S.P.Q.2d at 1943 & 1944 (citations omitted; italics in original).

That is exactly the case here since it is respectfully submitted that the Office Action reflects hindsight reconstruction and speculation, which these cases have indicated does not constitute evidence that will support a proper obviousness finding.

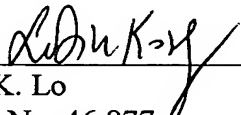
For at least these reasons, it is respectfully submitted that claims 1-27 are not obvious over Ott *et al.* in view of Tomita *et al.* or Vanek *et al.* Accordingly, withdrawal of the rejection of claims 1-27 under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

Applicants respectfully that a timely Notice of Allowance be issued in this case. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is urged to telephone the undersigned at (212) 908-6018.

Respectfully Submitted,

Dated: May 13, 2004


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